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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/530,800	03/13/2006	Chaim M. Roifman	LYMF-P01-008	4283

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ROPES & GRAY LLP
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EXAMINER	
FINN, MEGHAN R	

ART UNIT	PAPER NUMBER
1614	

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07/15/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/530,800	ROIFMAN ET AL.	
	Examiner	Art Unit	
	MEGHAN FINN	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,12-16,47,53-64 and 66-69* is/are pending in the application.

4a) Of the above claim(s) *2,3,5,6,9,10,47,53-56, 61-64, and 66-68* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,7,8,12-16,57-60 and 69* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 April 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/05/06; 7/27/06; 5/10/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election with traverse of group I (claims 1-10, 12-16, 53-64, and 66-69) in the reply filed on April 07, 2008 is acknowledged. The traversal is on the ground(s) that examining group II, directed towards a medical device comprising the compound of formula I would present no significant burden to the examiner. The examiner disagrees, there is a burden presented by that additional examination. There are significant differences, both in searching and in examination of a method of treating versus a device. Prior art that would be applicable to one invention would not necessarily be applicable to the other, and the searches are divergent. Thus there is a burden on the examiner.

The requirement is still deemed proper and is therefore made FINAL.

Applicant has also elected a specific compound “CR4” as the species of compound from formula I, as well as breast cancer as the species of disease, and taxol as the second anti-cancer agent present. Thus claims 1, 4, 7-8, 12-16, 57-60 and 69 are pending examination.

Applicant has submitted an Information Disclosure Statement (IDS) on July 27, 2006. There are several references for which only the abstract was considered, because the abstract was the only portion of the reference in English. These are marked with the phrase “Abstract only”. Additionally, References CM thru CS had no

publication date and thus cannot be considered. References CR1, CY1, CG2, CI2, CF3, and CI3 were not in English, and no English abstract or summary was provided, and thus they could not be considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1, 4, 7-8, 12-16, 57-60, and 69 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In claims 1, 4, and 8, applicant claims a method of treating with the compounds of formula I, with an elected species of CR4, and “salt, solvate, prodrug, or hydrate thereof”. While the salt form of a compound is a well known and accepted modification to a compound, solvates, and prodrugs especially are not. One of skill in the art would not be able to determine, from the direction provided by applicant, what compounds would qualify as prodrugs and which ones would be expected to have similar or any efficacy. Applicant has cited a general reference "Design of Prodrugs” (page 23, [0087])

however this reference is a generic 'how to make prodrugs' which would be an invitation to synthesize potentially hundreds of compounds without any real knowledge of them being able to act as prodrugs. Claims 7, 12-16, 58-60, and 69 are dependent from claims 1, 4, and 8 and thus claims 1, 4, 7-8, 12-16, 57-60, and 69 lack written description of the invention.

Claims 1, 4, 7-8, 12-16, 57-60, and 69 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant has claimed a method of treating cancer, specifically breast cancer, with a compound of formula I, specifically CR4. Applicant has not provided the necessary direction such that one of skill in the art would be able to use CR4, or any of the other non-elected compounds, in order to treat an animal for cancer.

In addition, claims 57-60 claims treatment of animals which are "at risk for developing vascularized solid tumor", yet applicant has not defined how one of skill in the art would know who is at risk, nor have they shown how to prevent the disease by treating those who are merely at risk, before they develop it.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in *In re Wands*, 8 USPQ2d 1400 at

1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount of direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The amount of experimentation necessary is extremely large (1) due to the lack of direction provided (2) and while there are examples of how to make the elected compound, and some cell culture tests, there is no direction provided towards treatment of animals (3). The nature of the invention is treatment of cancer, including a specific cancer, breast cancer (4) which is a complex and unpredictable disease (7) for which not many treatments are known (5) and while the relative skill of those in the art is high (6) the breadth of the claims indicated by prodrugs and by the general claims to cancer is very large (8).

The language of the claims is not strictly limited to *in vitro* treatments and encompass treating patients and as such do not have support in the specification. There is insufficient disclosure to reasonably predict that the methods and compounds of the instant specification would treat breast cancer *in vivo*. This is merely an unsubstantiated assertion with no evidence to support the contention that the *in vitro* studies of the specification are indicative of *in vivo* activity. Applicant has only shown cell culture data, not treating affected patients or shown an art recognized correlation between the data shown and the scope of the claimed invention. The artisan would

recognize and appreciate that there is no known correlation between *in vitro* and *in vivo* results, because the artisan recognizes that an *in vitro* assay cannot duplicate the complex conditions of *in vivo* therapy. In addition, variables such as biological stability, half-life, or clearance from the blood are important parameters in achieving successful therapy. The composition may be inactivated *in vivo* before producing a sufficient effect, for example, by immunological activation. In addition, the composition may not reach the target cells because of its inability to penetrate tissues or cells where its activity is to be exerted, may be absorbed by fluids, cells, and tissues where the composition has no effect and/or a large enough local concentration may not be established. There are no specific teachings in the disclosure that would allow one to have a reasonable expectation of success in transferring the *in vitro* method to treat affected patients. One is only left with speculation and an invitation to experiment. Therefore, the claimed invention lacks an enabling disclosure.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 4, 7-8, 12-16, 57-60 and 69 are rejected under 35 U.S.C. 103(a) as being unpatentable over Roifman et al (WO 01/79158 A2, cited on applicant's IDS) in view of Bessette et al. (US 2003/0017215 A1) in further view of Butler et al. (US 5,486,457).

Applicant is claiming a method of inhibiting vascular endothelial growth factor and treating breast cancer in animals by administering a compound of formula I, specifically CR4, with taxol as a second anti-cancer agent. Roifman et al. teaches treatment of cancer (abstract) and specifically teaches CR4 (page 19, line 1 and figures 1-7, page 6). Roifman et al. teaches that their invention is useful for inhibiting cell proliferation, and thus in treatment of many different cancers (page 4, line 26 thru page 5 line 15), however they do not teach breast cancer specifically Bessette et al. teaches that breast cancer is directly tied to cell proliferation (page 1, [0003]) and thus it would have been obvious to one of ordinary skill in the art at the time of the invention that the method of

Roifman et al. would be useful for breast cancer in addition to the cancers named as the compounds are shown to inhibit cell proliferation and cell proliferation is also linked to breast cancer. Neither Roifman nor Bessette et al. teach taxol, however taxol is a well known anti-cancer drug and Butler et al. teaches that taxol is useful for treatment of breast cancer (column 13, lines 55-65). Thus it would have been obvious to one of ordinary skill in the art at the time of the invention that taxol could be added to the therapy of Roifman et al. to treat breast cancer. It is commonly practiced in the cancer treatment art to combine different drugs which are known to treat cancer, especially the same cancers in order to achieve better therapy results. Thus claims 1, 4, 7-8, 12-16, 57-60 and 69 are unpatentable over Roifman et al. in view of Bessette et al. in further view of Butler et al.

Conclusion

No claims are allowed.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic

Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Meghan Finn whose telephone number is (571) 270-3281. The examiner can normally be reached on 7:30am-5pm Mon-Thu, 7:30am-4pm Friday (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Meghan Finn

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614